REMARKS

In view of the foregoing amendments, reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §112 are respectfully requested. By the present amendments, the claims have been amended to correct formalities. Additionally, new dependent claims are presented, which find support in the originally filed claims.

The specification has been amended to correct formal issues.

Turning now to the Official Action, the objection to the specification is noted. This objection is believed to be moot in view of the present amendments. As well, the objection to the Declaration is noted. A new Declaration will be submitted in due course.

Claims 1-2, 5-9, 14, 24-29, 37, 41, 45 and 46 stand objected to for assertedly being drawn to non-elected invention or depending on non-elected claims. These objections are believed to be rendered moot by the present amendments. Thus withdrawal of the objections is respectfully requested.

Claims 1, 2, 4, 5-9, 24-29, 34, 36, 37, 45 and 46 stand rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness. This rejection is respectfully traversed for at least the following reasons.

Claims 1, 24, 37 and 45 have been object to for not including a resolution step. The claims have now been amended to include in step (v) the recitation "thereby producing said heterodimers." Moreover, in light of the present amendments, the objection to the recitation "allowing sufficient time" in claims 1 and 24 is believed to be rendered moot and withdrawal thereof is respectfully requested.

In the Official Action, it is objected to step (vi) for reciting "optionally terminating." Step (vi) has been removed from the independent claims and rewritten in new dependent claims. Thus, it is believed that this objection is rendered moot and withdrawal thereof is respectfully requested.

In the Official Action it is objected to the recitation "desired binding

very clear and definite. The binding specificity of the antibodies is [illegible] essential limitation of the invention. Any antibody that binds to an antigen with

specificity can benefit from the method of dimerization covered by the subject invention. Those of skill in the art are amply aware of methods and techniques to determine whether an antibody specifically binds to an antigen.

The Official Action also objects to the recitation "introducing at least one cysteine codon." It is alleged that the exact meaning of the phrase is not clear. Applicants strenuously traverse this objection as the recitation is believed to be clear and definite. "At least one cysteine codon" means one or more cysteine codons. Moreover, the specification presents ample description on how to introduce a cysteine codon or codons in the DNA coding for antibodies such that two antibody molecules may be linked to form an antibody dimer according to the invention. Withdrawal of this rejection is respectfully requested.

The Official Action also objects to the recitation "partially reduce the intra or inter molecular disulfide bonds of said antibody molecule." In particular, the Official Action queries as to what inter or intra molecular disulfide bonds are reduced. As discussed throughout the specification, for example in the paragraph bridging pages 14 and 15, placement of an engineered cysteine in the heavy chain, for example at position 444, may result in intrachain disulfide formation. To benefit from the advantages of the subject invention, the cysteine linker in one of the antibody molecules is partially reduced before dimerization can proceed. Applicants have chosen to partially reduce the antibody molecules, for example by using dithiothreitol (DTT) in order to selectively expose specific thiols. Moreover, Example 2 clearly explains how the partial reduction is practiced in conjunction with the antibody C2B8. Thus, the objection is improper and should be withdrawn

The recitation "thereby enhance the function of antibody dimers" was objected to for alleged lack of clarity. The term "function" was inadvertently recited instead of the term "formation." By the above amendments, the term function has been replaced with the term formation. This correction is at least implicitly supported throughout the specification. It is respectfully submitted that the objection has been rendered

that the specification in light of the record in the subject application provide ample

guidance to those of skill in the art to recognize the heterodimer C2B8/p5E8 as claimed in the present application. In particular, it is submitted that US Patent No. 5,830,698 cited in the subject specification and US Patent No. 6,011,138 cited by the Examiner provide extensive discussion of the C2B8 and the p5E8 antibody molecules. Moreover, Figure 4 and the discussion thereof in the specification provide an illustration of how the C2B8 and p5E8 molecules are combined to provide antibody heterodimers in accordance with the subject invention. Thus, withdrawal of the objection is respectfully requested.

The Official Action queries as to the meaning of the recitation "light chain of desired specificity." As discussed above, the dimer molecules prepared according to the invention are the result of the combination of two antibody molecules, each antibody molecule having a binding specificity defined by the combination of its heavy and light chains.

As to the objection to the recitation "antibody dimer" it is respectfully submitted that the specification and claims are clear in regards to the nature of the antibody dimers of the invention. It is clear that those antibody dimers have two antibody molecules that are linked to form the dimer.

Claims 5 and 9 have been revised to replace the recitation "capable of." Thus the objection of the recitation in those claims of the term "capable of" is believed to be rendered moot and withdrawal thereof is respectfully requested.

Claims 1, 2, 4, 5-9, 24-29, 34, 36, 37, 45 and 46 stand rejected under 35 U.S.C. §112 first paragraph for alleged non-enabling specification. This rejection is respectfully traversed for at least the following reasons.

At the outset, Applicants note the acknowledgement in the Official Action that the subject specification is enabling for a method for producing a IgG antibody heterodimer with antibodies which specifically bind CD20 and CD23. However, Applicants strenuously traverse the conclusion reached in the Official Action that the specification does not enable any person skilled in the

respectfully submitted that those of skill in the art will recognize that the

subject invention relates to antibody dimers that are formed by connecting two (2) antibody molecules, each molecule having binding affinity to an antigen. The binding affinity of the two molecules forming the dimer may be to the same antigen (homodimer) or two different antigens (heterodimer) as is claimed in the subject application. The specification in its entirety, and particularly the examples provide ample guidance on how to prepare dimers according to the invention such that the resulting heterodimer is prepared at a high purity and with relatively high yields.

In addition, Applicants submit that the Examiner's position that "undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone" is improper in view of the standards for enablement, as addressed by the CAFC in the case of *in re Brana*, 551 F.3d 1560; 34 U.S.P.Q.2d 1437 (CFC, decided March 30, 1995). In *in re Brana*, the CAFC held that:

> A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statement contained therein which must be relied on for enabling support. *In re Marzocchi*, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure.

In summary, the essence of the court's decision was that if the patent disclosure contains a teaching of how to make and use an invention which is commensurate with the scope of the claims and further provides a specific

unless there is reason to doubt the objective truth of the statements contained in

the disclosure which are relied on for enabling support. Applicants submit that the present disclosure fully satisfies the enablement standard set forth in *in re Brana* in that it provides sufficient teaching of how to make the antibody heterodimers of the invention.

As to the objection to Claim 41 for reciting a pharmaceutical composition, it is respectfully submitted that the biological activity of the antibody dimers of the invention is clearly demonstrated in the specification, particularly in Examples 5-12. The demonstrated biological activity of the antibody dimers of the invention in conjunction with well known methods of formulating pharmaceuticals, as indicated in page 20 of the specification, provide ample guidance for those skilled in the art to prepare pharmaceutical compositions as claimed in Claim 41. Withdrawal of this objection is respectfully requested. As to the objection to Claim 35, as discussed above, the antibodies demonstrated in the subject specification are well identified in the art, in particular those of skill in the art have access to US Patent 5,830,698 and 6,011,138 which are of record in the subject application.

In light of the foregoing, it is respectfully submitted that the specification and claims are free of the rejections under 35 U.S.C. §112 first and second paragraphs. Thus, withdrawal of the rejections is in order and respectfully requested.

Prior to addressing the art rejections set forth in the Official Action, Applicants submit the following summary of the invention and the advantages thereof. As extensively discussed in the specification, the present invention generally relates to a process for the preparation of biologically active antibody dimers and pharmaceutical compositions containing such antibody dimers. The process of the invention provides numerous advantages. For example, the

antibody dimers. In part, the advantages of the invention are obtained by using monoclonal antibodies which had had a cysteine residue genetically engineered

at a specific site on the F_c arm of the antibody, thereby eliminating the need to chemically introduce the reactive group. As indicated in the specification, yields of homodimer formation of between 40 to 50% of the starting material are obtained with the method of the invention. Also, surprisingly and unexpectedly, when compared to antibody dimers made by conventional methods, dimers produced by the claimed process were capable of initiating apoptosis in proliferating malignant B-cell populations. More importantly, the dimers of the invention were strongly growth inhibitory for lymphoma cells in culture, showing a two hundred fold increase in potency compared to that of a dimer prepared according to conventional methods.

The dimers of the invention are obtained by coupling monomeric monoclonal antibodies. The methods of the present invention produce either dimers formed by disulfide bonds or dimers formed by thioether linkage. In the case of disulfide bonds, the bonds form naturally between the thiol groups on the cysteine. For thioether linkage, a maleimido cross-linker (which is thiol reactive) is added to the antibodies which forms a bridge between the two antibody molecules. The cross-linkers bind on one side of a thiol group and on the other side to any of a variety of molecules (for example, lysine, carboxyl group, etc.) which are naturally present on an antibody molecule. In this way, a dimer can be formed between an antibody which has been modified to contain a cysteine molecule at a specific position and another antibody which has not been modified. By using special conditions (i.e., purifying the selectively reduced monoclonal antibody by applying it to PD-10: and equilibrating with the oxygenated normal saline containing sodiumcitrate, which discourages the formation of homodimer via disulfide bond) one can be assured that only dimers formed by thioether linkage are produced.

invention produces very little, if any, naturally occurring dimers, and thus obtains a high yield of the desired dimer.

Returning to the Official Action, Claims 2, 4, 28, 41 and 46 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Brenner et al. (*Science* 299: 81-83 (1985)). This rejection is respectfully traversed for at least the following reasons.

Brenner does not disclose each feature in the present invention. For example, Brenner et al. does not disclose an antibody dimer formed by linking two antibody molecules. For example, as shown on Figure 1, Brenner et al. discloses fragmenting antibody molecules to obtain fragments from two different antibodies (i.e., antibody molecules having different specificities) and reconstituting an antibody molecule by linking two fragments, each from one antibody molecule. The result is an antibody molecule having dual specificity due to fragments obtained from the two different antibody molecules. In contrast, the present invention relates to the formation of antibody dimers obtained by linking two antibody molecules. Accordingly, Brenner et al. does not anticipate the present invention. Thus, the rejection under 35 U.S.C. §102(b) based on Brenner et al. should be withdrawn and such favorable action is respectfully requested.

Claims 1, 2, 4-9, 14, 24-29, 34-37, 41 and 45-46 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Caron et al. (*J. Exp. Med.* 176: 1191-1195 (1992)) and further in view of Fanger et al. (*Critical Review in Immunology* 12: 101-124 (1992)) and Cumber et al. (*J. of Immunol.* 149: 120-126 (1992) and Reff et al. [a] (US Patent No. 6,011,138) and Reff et al. [b] (Blood 83: 435-445 (1994)). This rejection is respectfully traversed for at least the following reasons.

Caron et al. does not disclose or suggest each feature of the present invention. For example, Caron et al. does not disclose or suggest antibody

reduce the intra or inter molecular disulfide bonds of said antibody molecule to enhance the formation of antibody dimers. Moreover, none of the Fanger et

al., Cumber et al., Reff et al. [a] or Reff et al. [b] cures the deficiencies of Caron et al., as none of those documents discloses or suggests contacting a purified antibody molecule with an amount of suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of the antibody molecule. Moreover, neither Caron et al. nor the secondary references, appreciates the advantages of contacting the purified antibody molecule with a suitable reducing agent in an amount sufficient to partially reduce the intra or inter molecular disulfide bonds of the antibody molecule.

Caron et al. is relied upon as disclosing a method of producing dimeric IgG which assertedly comprises converting by recombinant DNA mutagenesis the serine at position 444 in the heavy chain to a cysteine. While the Official Action acknowledges that Caron et al. does not teach a heterodimer, adding a thiol reactive group introduced on another antibody, an anti-CD23 antibody or an anti-CD20 antibody, the Official Action asserts that those deficiencies are made up by the teachings of Fanger et al., Cumber et al. and Reff et al. [a] and [b].

Fanger et al. is relied upon for its asserted teaching of bispecific antibodies formed by chemical cross-linking or by molecular genetic approaches. Cumber et al. is relied upon based on its asserted disclosure relating to bispecific antibody produced by chemical cross-linking with a maleimido group with the cysteine residues wherein one is introduced in the heavy chain. Reff et al. [a] is relied upon for the disclosure of anti-CD23 antibody (p5E8) and Reff et al. [b] is relied upon based on the disclosure therein of the anti-CD20 antibody (C2B8). While Applicants submit that the references of record are devoid of the requisite motivation to combine the teachings thereof as hypothesized in the Official Action, it is submitted that

fails to disclose the step of contacting the purified antibody molecule with an amount of suitable reducing agents sufficient to partially reduce the intra or

inter molecular disulfide bonds of the antibody molecule. Moreover, all the references fail to appreciate the advantages of providing such a reducing agent.

Thus, there is no *prima fascia* case of obviousness against the present claims based on Caron et al. alone or in combination with Fanger et al., Cumber et al., Reff et al. [a] and Reff et al. [b]. Accordingly, the rejection under 35 U.S.C. §103(a) based on those documents should be withdrawn and such favorable action is respectfully requested.

From the foregoing, it is anticipated that this response should place this case in condition for allowance. A notice to that effect is respectfully solicited. However, if any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,
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APPENDIX

In the Specification:

Page 22, please delete the paragraph beginning at line 8 and replace it with the following paragraph:

Through the use of conventional in vitro site directed mutagenesis, applicants effected a transversion mutation C to G within the plasmid DNA (Figure 3). This IDEC proprietary expression construct (Reff et al., U.S. Patent Appl. Serial No. 08/819,866, filed March 14, 1997, now US Patent No. 5,830,698) encodes the anti-CD20 immunoglobulin light and heavy chains, as well as sequences necessary for homologous integration into a proprietary CHO cell line Reff et al. IBID), followed by dominant selection with G418 and/or methotrexate. The affect of this nucleotide mutation is to change the codon second base, thereby encoding a cysteine residue substituted for the normal serine residue at position 445 near the gamma 1 heavy chain carboxyl terminus (see Figure 2).

In the Claims:

Please enter the following amended Claims:

1. (Amended) A method for producing an antibody heterodimer [dimer] comprising:

(i) obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has a desired binding specificity and introducing at least one cysteine codon therein via recombinant DNA mutagenesis;

(ii) expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes an antibody molecule light chain of desired specificity, to produce an antibody molecule

expression system.

(iv) contacting said purified antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and thereby enhance the [function] formation of antibody dimers; and

(v) allowing sufficient time for the dimerization reaction to proceed; thereby producing said antibody heterodimer. [and

(vi) optionally terminating the reducing reaction by the addition of cysteine or after thiol blocking reagent.]

5. (Amended) The method of Claim 1, which results in an IgG/IgG dimer [capable of activating] which activates components of the complement system.

7. (Amended) The method of Claim 1, which results in an IgG/IgG dimer that [is capable of binding] binds to Fcγ receptors on cytotoxic effector cells.

9. (Amended) The method of Claim [2] 1 which results in an IgG/IgG dimer [capable of initiating] which initiates programmed cell death (apoptosis).

24. (Amended) A method for producing an antibody heterodimer [dimer] comprising:

(i) obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has a desired binding specificity and introducing at least one cysteine codon therein via recombinant DNA

expression system, together with a DNA molecule that encodes an antibody

molecule light chain of desired binding specificity, to produce an antibody molecule containing said introduced cysteine residue;

(iii) purifying said antibody molecule from said host cell or expression system;

(iv) contacting said purified antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and thereby enhance the [function] formation of antibody dimers; and

(v) adding a thiol reactive group introduced on another antibody molecule which does not have a cysteine group introduced therein and allowing sufficient time for the dimerization reaction to proceed thereby producing said antibody heterodimer[; and

(vi) optionally terminating the reducing reaction by the addition of cysteine.]

28. (Amended) An IgG/IgG dimer produced by the method of Claim [23] 22, wherein said IgG's are of the same or different IgG subclass.

37. (Amended) A method for producing an antibody heterodimer [dimer] comprising:

(i) obtaining a DNA molecule that encodes an antibody molecule heavy chain that has a desired binding specificity and introducing at least one cysteine codon therein via site specific mutagenesis;

(ii) expressing said DNA molecule in a suitable host cell, together with a DNA molecule that encodes an antibody light chain, to produce an antibody molecule containing said introduced cysteine residue;

of a suitable reducing agent sufficient to partially reduce the intra or inter

molecule disulfide bonds of said antibody molecule and thereby enhance the [function] formation of antibody dimers; and

(v) cross-linking the reduced antibody molecules using a BIS-maleimido cross-linker thereby producing said antibody heterodimer.[;

(vi) optionally terminating the reducing reaction by the addition of cysteine.]

41. A pharmaceutical composition comprising an IgG/IgG dimer according to Claim [28] 22, and a pharmaceutically acceptable carrier.

45. (Amended) A method for producing an IgG/IgG dimer comprising genetically engineering a first IgG MAb to introduce a cysteine molecule placed in a position which inhibits or prevents formation of an intramolecular disulfide bridge between sister heavy chains on the same antibody molecule and exposing said first MAb to a second IgG MAb to produce said IgG/IgG dimer.

46. (Amended) An IgG/IgG dimer produced by the method of Claim [44] 45.

47. (New) The method of Claim 1, further comprising

(vii) terminating the reducing reaction by the addition of cysteine or other thiol blocking reagent.

48. (New) The method of Claim 24, further comprising

49. (New) The method of Claim 37, further comprising

(vi) terminating the reducing reaction by the addition of cysteine or other thiol blocking reagent.